

elicited after HCV infection [Farci et al., *Science* **258**, 135-140 (1992); Prince et al., *J. Infect Dis.* **165**, 438-443 (1993)] present major challenges towards these goals.—

***In The Claims:***

Please amend the claims as indicated:

Cancel claims 10, 11, 18-24, 41-44 and 63-68.

1. (Four times amended) A polynucleotide comprising a non-naturally occurring HCV sequence that is capable of productive replication in a host cell, or is capable of being transcribed into a non-naturally occurring HCV sequence that is capable of productive replication in a host cell, wherein the HCV sequence comprises, from 5' to 3' on the positive-sense nucleic acid, a functional 5' non-translated region (5' NTR); one or more protein coding regions, including at least one polyprotein coding region that is capable of replicating HCV RNA; and a functional HCV 3' non-translated region (3' NTR), wherein said polynucleotide further comprises an adaptive mutation in the NS5A coding region that confers improved cell culture characteristics to said polynucleotide.

12. (Amended) The polynucleotide of claim [11] 1, wherein the mutation is within 50 nucleotides of an interferon sensitivity determining region (ISDR) or includes the ISDR.

24. (New) The polynucleotide of claim 1, further comprising a mutation in the NS3 or NS4B coding region.